AMENDMENTS TO THE DRAWINGS

The attached drawing includes a change to Fig. 1. The mechanical loading mechanism had not been shown in the drawings before, as described in paragraph [0040] of the specification. This feature has now been added to Fig. 1 in schematic form. Paragraph [0040] of the specification has also been modified to delete the phrase "not shown" and identify this apparatus with reference numeral 30. This sheet, which includes Fig. 1 replaces the original sheet including Fig. 1. No new matter has been added. An Annotated Sheet is attached to show the change and a Replacement Sheet is also attached.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

REMARKS

The Office Action, dated May 3, 2009, has been reviewed and the Examiner's comments carefully considered. The present Amendment modifies claims 1, 36, and 69, and adds new claims 70-72, all in accordance with the originally-filed specification. No new matter has been added. Further, claim 30 has been cancelled, without prejudice. Accordingly, claims 1-5, 7-9, 11, 18-20, 22, 23, 25, 31, 32, 36-39, 41, 43, 44, 46, 53-55, 65-67, and 69-72 are pending in this application, and claims 1, 36, and 69-72 are in independent form.

The Examiner is thanked for considering the amendments and arguments presented in an Amendment, dated December 18, 2008 (which was responsive to the previous Office Action of September 19, 2008). In particular, the Examiner believes that the amendments and arguments were rendered moot in view of certain new grounds of rejections. Claims 1-5, 7-9, 11, 18-20, 22, 23, 25, 30-32, 36-39, 41, 43, 44, 46, 53-55, 65-67, and 69 stand rejected under 35 U.S.C. § 103(a) as being obvious over the previously-cited Guiliano patent (U.S. Patent No. 6,416,959) in view of the newly-cited U.S. Patent No. 6,881,584 to Lenhard et al. In view of the foregoing amendments and the following remarks, Applicants respectfully request reconsideration of these rejections.

Summary of the Preferred Embodiments

In one preferred embodiment, and as set forth in independent 1, as amended, the present invention provides a tissue engineered construct analytical imaging system for use in connection with at least one culture well having a tissue engineered construct therein and positionable in an enclosed environment. The system includes an imaging device positioned within the enclosed environment and configured to obtain three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the enclosed environment. The system further includes a computer controller configured to at least one of: (i) receive data from the imaging device; (ii) analyze the data for determining at least one of the following: matrix organization, matrix compaction, matrix contraction, response to loading, or any combination thereof, the three-dimensional image data; and (iii) output data reflecting results of an analysis; wherein the tissue engineered construct is at least one of the

following: a bioartificial cellular tissue construct, bioartificial tissue, and a bioartificial tendon.

In a further preferred embodiment, as set forth in independent claim 36, as amended, the present invention is directed to a computer-implemented method of obtaining and analyzing images of a tissue engineered construct. The method includes: (a) positioning at least one culture well having the tissue engineered construct therein in an enclosed environment; (b) obtaining, from an imaging device positioned within the enclosed environment, three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the enclosed environment, and wherein the tissue engineered construct is at least one of the following: a bioartificial cellular tissue construct, bioartificial tissue, and a bioartificial tendon; (c) analyzing the three-dimensional image; and (d) determining at least one of the following: matrix organization, matrix compaction, matrix contraction, response to loading, or any combination thereof.

In a further embodiment, and as set forth in independent claim 69, the present invention provides a tissue engineered construct imaging and analysis apparatus for use in connection with at least one culture well having tissue engineered constructs therein and positionable in an enclosed environment. The apparatus includes: imaging means positionable in the enclosed environment and for obtaining three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the enclosed environment, and wherein the tissue engineered construct is at least one of the following: a bioartificial cellular tissue construct, bioartificial tissue, and a bioartificial tendon; and computing means for receiving and analyzing the three-dimensional data, and determining at least one of the following: matrix organization, matrix compaction, matrix contraction, response to loading, or any combination thereof.

In another embodiment, and as set forth in new independent claim 70, the present invention is directed to a tissue engineered construct analytical imaging system for use in connection with at least one culture well having a tissue engineered construct therein and positionable in an enclosed environment. The system includes: an imaging device positioned within the enclosed environment and configured to obtain three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the

enclosed environment, wherein the tissue engineered construct is anchored on at least two edges thereof; a mechanical loading mechanism configured to apply a load to the tissue engineered construct; and a computer controller configured to: (i) receive data from the imaging device; (ii) analyze the data and determine a response to a load applied by the mechanical loading mechanism to the tissue engineered construct within the well area of interest; and (iii) output data reflecting results of the analysis.

In a further embodiment, and as set forth in new independent claim 71, the present invention provides a computer-implemented method of obtaining and analyzing images of a tissue engineered construct. This method includes: (a) positioning at least one culture well having the tissue engineered construct therein in an enclosed environment; (b) anchoring the tissue engineered construct on at least two edges thereof; (c) applying a load to the tissue engineered construct; (d) obtaining three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the enclosed environment; (e) analyzing the three-dimensional data; and (f) determining a response to the applied load.

In a still further embodiment, and as set forth in new independent claim 72, the present invention is directed to a tissue engineered construct imaging and analysis apparatus for use in connection with at least one culture well having tissue engineered constructs therein and positionable in an enclosed environment. The apparatus includes: imaging means positionable in the enclosed environment and for obtaining three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the enclosed environment, wherein the tissue engineered construct is anchored on at least two edges thereof; loading means for applying a load to the tissue engineered construct; and computing means for receiving and analyzing the three-dimensional data, and determining a response to the applied load.

The Cited Prior Art

The Giuliano patent is directed to a system for cell-based screening. With reference to Fig. 1 of the Giuliano patent, an inverted fluorescence microscope (1) is used to obtain images of materials in a plate (4), which is movable using an XY stage (3), in

particular, a joystick (6) allows for the manual movement of the stage in various directions. A high resolution digital camera (7) acquires images from each well or location on the plate, and an automated controller (9) and central processing unit (10) allow for the various control aspects of the system. The software provides movement of the Z-axis motor drive (5) in small steps, where the step distance is user selected to account for a wide range of different nuclear diameters. The Examiner admits that the Giuliano patent does not teach the positioning of the imaging device inside the incubator.

The newly-cited Lenhard patent is directed to infrared thermography systems and methods. The Examiner refers to Fig. 1 of this reference, which appears to include an imaging device (1) in an incubator (2).

The Cited Prior Art Does Not Teach or Suggest the Systems, Methods, or Apparatus of the Claims

Applicants have addressed the Giuliano patent in connection with the previous version of the claims in the Amendment of December 18, 2008. The remarks and comments made in that Amendment are incorporated herein by reference.

Applicants have amended independent claims 1, 36, and 69 in order to additionally address the Examiner's rejections and move this case towards allowance. In particular, these independent claims (1, 36, and 69) have been amended to specifically set forth the determinations made in accordance with the analysis of the three-dimensional image data obtained from the imaging device. Based upon this image data, the computer controller determines matrix organization, matrix compaction, matrix contraction, and/or response to loading. Still further, and in the claimed embodiments set forth in independent claims 1, 36, and 69, the tissue engineered constrict is a bioartificial cellular tissue construct, bioartificial tissue, or a bioartificial tendon.

First, neither the Giuliano patent nor the Lenhard patent teaches or suggests the system, method, or apparatus of claims 1, 36, and 69, all of which include the imaging device positioned within the enclosed environment for obtaining data without removal of the culture well, where the three-dimensional image data is analyzed and a determination is made of matrix organization, matrix compaction, matrix contraction, and/or response to loading, and where the tissue engineered construct is a bioartificial cellular tissue construct, bioartificial tissue, or a bioartificial tendon. Such determinations provide invaluable

information to the user in the creation and analysis of genetic material. While such measurements and determinations were previously made manually by periodically removing culture plates from the controlled environment, the present invention provides a unique system and arrangement for allowing these important determinations to be made automatically and based upon the three-dimensional image data, which is obtained without the removal of the culture well from the enclosed environment. In addition, such measurements are particularly useful in connection with bioartificial materials, e.g., bioartificial cellular tissue constructs, bioartificial tissues, bioartificial tendons, etc. None of the prior art teaches or suggests the use and analysis in connection with this particular type of cellular material, and certainly not the type of analytical determinations set forth in independent claims 1, 36, and 69, as amended.

Accordingly, Applicants respectfully submit that none of the Guiliano patent, the Lenhard patent, nor any of the prior art of record, whether used alone or in combination, teaches or suggests *inter alia*: a tissue engineered construct analytical imaging system that includes a computer controller configured to "analyze the data for determining at least one of the following: matrix organization, matrix compaction, matrix contraction, response to loading, or any combination thereof," and "wherein the tissue engineered construct is at least one of the following: a bioartificial cellular tissue construct, a bioartificial tissue, and a bioartificial tendon" (claim 1); a computer-implemented method of obtaining and analyzing images "wherein the tissue engineered construct is at least one of the following: a bioartificial cellular tissue construct, a bioartificial tissue, and a bioartificial tendon" including the steps of "(c) analyzing the three-dimensional image; and (d) determining at least one of the following: matrix organization, matrix compaction, matrix contraction, response to loading, or any combination thereof" (claim 36); or a tissue engineered construct imaging and analysis of apparatus with imaging means positionable in the enclosed environment for obtaining three-dimensional image data, "wherein the tissue engineered construct is at least one of the following: a bioartificial cellular tissue construct, a bioartificial tissue, and a bioartificial tendon" and "computing means for receiving and analyzing the three-dimensional data, and determining at least one of the following: matrix organization, matrix compaction, matrix contraction, response to loading, or any combination thereof" (claim 69). Therefore, for at least these reasons, independent claims 1, 36, and 69 are not taught or suggested in the prior art of record.

When dealing with certain tissue engineered constructs, the cells that are cultured in three-dimensional collagen gels express a more native state phenotype, since these cells form a syncidial network that is capable of being mechanically loaded. Accordingly, in certain analytical instances, a mechanical load is applied to such tissue engineered constructs, e.g., bioartificial cellular tissue constructs. Such mechanical loading may be achieved by various mechanisms, such as by an arrangement including a loading post placed beneath each well, where a vacuum is used to displace the flexible membrane downward. This results in a uniaxial strain on the tissue construct, such that the cells may be cultured in a mechanically active and three-dimensional culture environment, which is particularly useful in the field of tissue engineering.

New claims 70-72 are directed to a system, method, and apparatus that includes and integrates this unique anchoring and loading function and feature. In particular, the tissue engineered construct is anchored on at least two edges, and a mechanical loading mechanism or means applies a load to this tissue engineered construct. The three-dimensional image data is obtained (as discussed above), and without the removal of the culture well from the enclosed environment, and provided to a computer controller. The controller analyzes the data and determines a response to the load applied by the mechanical loading mechanism or means. This provides valuable information in the field of tissue engineering.

None of the Giuliano patent, the Lenhard patent, nor any of the cited prior art, includes the claimed system, method, and arrangement with this unique loading and analysis feature. The Examiner appears to indicate that mechanical loading may occur during the step 305 in Fig. 11 of the Giuliano patent. Applicants disagree. Step 305 in this reference relates to the dispensing of fluids into wells in the plate. Specifically, the Giuliano patent indicates that an optional fluid delivery device 305 (*see* Fig. 8) is controlled by the system to dispense fluids into the wells during the scan. With reference to Fig. 8, this fluid delivery step is for use in connection with a live cell embodiment of the cell screening method. Syringes 702 are attached via flexible tubing 703 to pipette tips 705 to deliver fluid to each well, which is simply a means for delivering reagent to all the wells on the plate. This has no relation to or bearing upon the *mechanical* loading of the tissue engineered construct. Instead, this portion of the Giuliano patent simply relates to the provision of reagent to a cell culture via a fluid dispensing system.

In any case, Applicants again assert that the prior art of record does not teach or suggest the system, method, or apparatus of new independent claims 70-72. Specifically, none of these prior art references disclose, *inter alia:* a tissue engineered construct analytical imaging system that includes the described imaging device "wherein the tissue engineered construct is anchored on at least two edges thereof" and includes "a mechanical loading mechanism configured to apply a load to the tissue engineered construct; and a computer controller configured to: (i) receive data from the imaging device; (ii) analyze the data and determine a response to a load applied by the mechanical loading mechanism to the tissue engineered construct within the well area of interest; and (iii) output data reflecting results of the analysis" (claim 70); a computer-implemented method of obtaining and analyzing images of a tissue engineered construct including: "anchoring the tissue engineered construct on at least two edges thereof," "applying a load to the tissue engineered construct," "obtaining three-dimensional image data reflective of at least a portion of the tissue engineered construct in a well area of interest in the at least one culture well, without the removal of the culture well from the enclosed environment," "analyzing the three-dimensional data," and determining a response to the applied load" (claim 71); and a tissue engineered construct imaging and analysis apparatus including an imaging means positionable in the enclosed environment for obtaining three-dimensional image data "wherein the tissue engineered construct is anchored on at least two edges thereof," and including "loading means for applying a load to the tissue engineered construct," and "computing means for receiving and analyzing the three-dimensional data, and determining a response to the applied load" (claim 72). Accordingly, it is submitted that none of the Giuliano patent, Lenhard patent, nor any of the prior art of record, whether used alone or in combination, teaches or suggests the system, method, and apparatus of independent claims 70-72, as added.

<u>Summary</u>

For the foregoing reasons, independent claims 1, 36, and 69-72, as amended and added, are not anticipated by or rendered obvious over the Giuliano patent, the Lenhard patent nor any of the prior art of record, whether used alone or in combination. Reconsideration of the rejection of independent claims 1, 36, and 69 is respectfully requested. Claims 2-5, 7-9, 11, 18-20, 22, 23, 25, 31, and 32 depend either directly or indirectly from

and add further limitations to independent claims 1 and are believed to be allowable for at least the reasons discussed hereinabove in connection with independent claims 1. Therefore, for all the above reasons, reconsideration of the rejections of claims 2-5, 7-9, 11, 18-20, 22, 23, 25, 31, and 32 is respectfully requested. Claims 37-39, 41, 43, 44, 46, 53-55, and 65-67 depend either directly or indirectly from and add further limitations to independent claim 36 and are believed to be allowable for at least the reasons discussed hereinabove in connection with independent claim 36. Therefore, for all the above reasons, reconsideration of the rejections of claims 37-39, 41, 43, 44, 46, 53-55, and 65-67 is respectfully requested.

For all the foregoing reasons, Applicants believe that claims 1-5, 7-9, 11, 18-20, 22, 23, 25, 30-32, 36-39, 41, 43, 44, 46, 53-55, 65-67, and 69-72, as amended and added, are patentable over the cited prior art and in condition for allowance. Reconsideration and allowance of all pending claims 1-5, 7-9, 11, 18-20, 22, 23, 25, 30-32, 36-39, 41, 43, 44, 46, 53-55, 65-67, and 69-72 are respectfully requested. To the extent the Examiner maintains these rejections in view of the arguments and discussion presented above, Applicant specifically requests an interview with the Examiner to discuss this matter, Applicant's position and to move this case towards allowance.

Respectfully submitted,
THE WEBB LAW FIRM

By ____________________

Nathan J. Prepelka
Registration No. 43,016
Attorney for Applicants
436 Seventh Avenue
700 Koppers Building
Pittsburgh, PA 15219
Telephone: (412) 471-8815
Facsimile: (412) 471-4094
E-mail: webblaw@webblaw.com

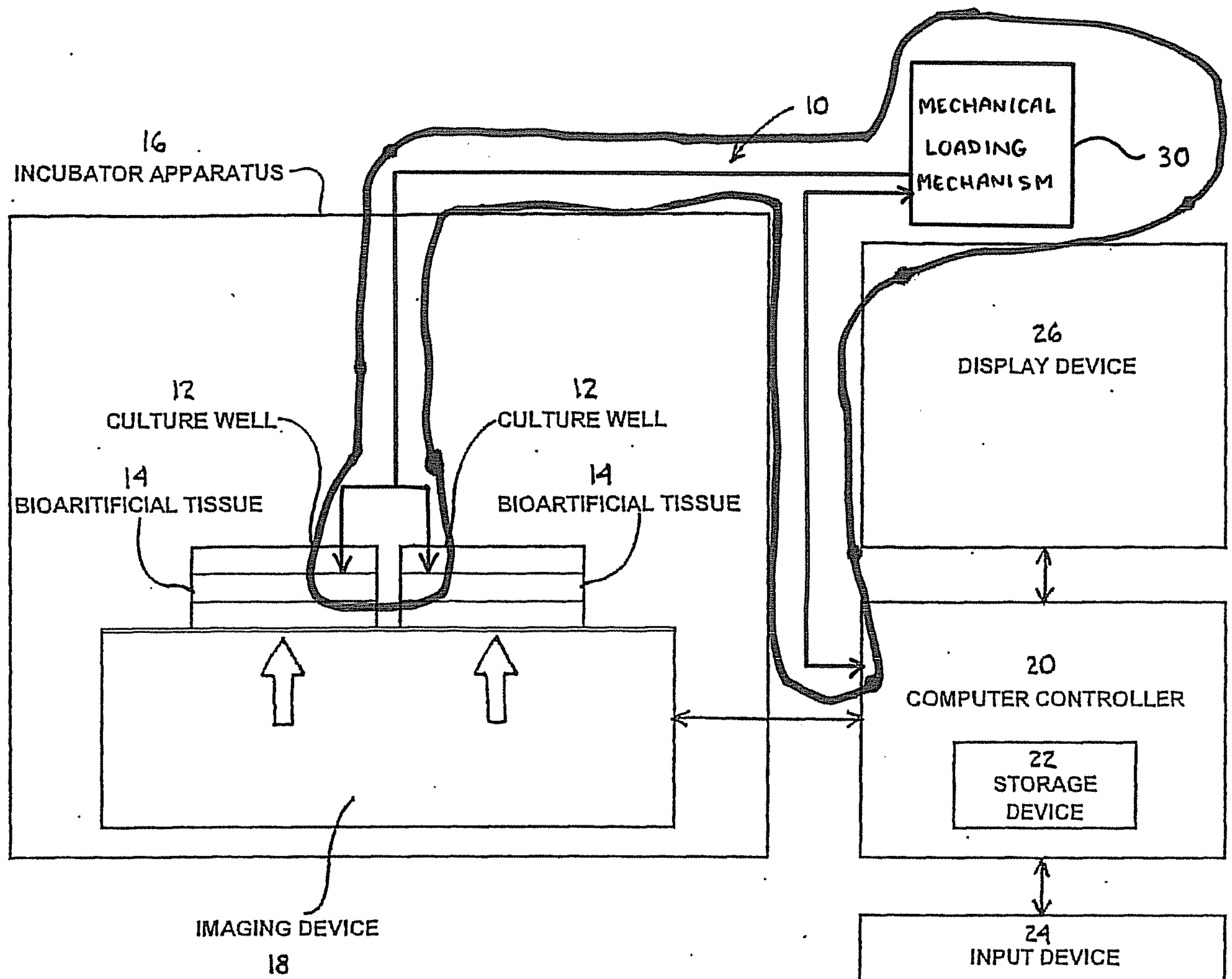
10
MECHANICAL LOADING MECHANISM
30
16
INCUBATOR APPARATUS
26
DISPLAY DEVICE
12
CULTURE WELL
12
CULTURE WELL
14
BIOARITIFICIAL TISSUE
14
BIOARTIFICIAL TISSUE
20
COMPUTER CONTROLLER
22
STORAGE DEVICE
IMAGING DEVICE
18
24
INPUT DEVICE

Fig. 1